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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/622,719	LOEWENHEIM, HUBERT	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,29,31-48,55-58 and 62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28, 29, 31-48, 55-58 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Receipt is acknowledged of the English translation of the parent Application PCT/EP99/01153, which is identical to the parent German Application No. 198 07 426.3. Priority to February 23, 1998 has been accorded to the instant application for all subject matter in German Application No. 198 07 426.3.

Claim Rejections - 35 USC § 112

The rejections of record of claims 28-61 under 35 USC 112, second paragraph are withdrawn in response to Applicant's amendments filed March 11, 2000, however, new rejections under 35 USC 112, second paragraph are set forth herein.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41, 44, 45 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 recites the limitation "the nucleic acid molecule". There is insufficient antecedent basis for this limitation in the claim, because claim 41 depends on claim 47, which does not recite a nucleic acid molecule.

Claim 44 recites the limitation "the virus" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 45 recites the limitation "the viral vector". There is insufficient antecedent basis for this limitation in the claim.

Claim 45 is further indefinite because it recites a viral vector that is a non-viral vector. It is unclear how a vector can be both viral and non-viral.

Claim 48 is indefinite because it recites an intended use for a composition used in a method. It is unclear if the claim limits the method of claim 28 to a method wherein the active ingredient is applied locally or if the active ingredient is one that can be used locally.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 29 is maintained as rejected and claims 28, 31-48, 55-58 and 62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance

presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 28, 29, 31-48, 55-58 and 62 are drawn broadly to methods of treating generally any disease or disorder of the inner ear linked with damage or destruction of the sensory cells by administering generally any active ingredient able to inhibit or eliminate the action of generally any cell cycle inhibitor in the inner ear. Claims 28, 29, 31-48, 55-58 and 62 encompass treatments for a broad range of diseases and conditions using a broad range of compounds, including antisense and gene therapy methods of treatment and would include methods wherein these compounds are administered directly to the ear (local administration) or systemically delivered compounds.

The specification provides examples wherein a $p27^{Kip1}$ knockout mouse is made and cells within the corti-organ of the mouse undergo cell division and these mice have more hair cells than normal mice. This example does not provide any demonstration of a treatment for any disease or disorder of the inner ear. There are no examples wherein any inhibitor of a cell cycle inhibitor is administered to a subject. There are no examples wherein any other cell cycle inhibitor (besides $p27^{Kip1}$) activity is knocked out or even reduced and sensory cell growth is affected. There are no examples wherein any disease or disorder of the inner ear is treated by inhibition of a cell cycle inhibitor. The specification does not provide any guidance on what specific diseases or disorders can be treated by inhibiting a cell cycle inhibitor, or what specific cell cycle inhibitor to target for inhibition to provide a treatment effect for a particular disorder or disease. There are

no examples wherein antisense a gene therapy vector is delivered in vivo (whole organism) nor wherein antisense or gene therapy methods are used to provide a treatment effect for any disease or disorder of the inner ear.

After the date the instant invention was made, the inventor of the instant application states, "A causal therapeutic option for sensorineural hearing loss is not yet available....A specific therapeutic modality directly applicable to the inner ear has yet to be developed." and "At present the only available therapeutic option is symptomatic in the form of hearing aids." (Pfister and Löwenheim, 2002, p53, center column).

The morphological development of the inner ear involves a complex series or developmental events (See for example, Chen et al.) and at the time the instant invention was made "the mechanisms that link developmental events to the cell cycle machinery that controls cell proliferation remain poorly understood" (Chen et al., p 1581, introduction, first column). Although cyclin-dependent kinase inhibitors were known to be involved in developmental events in the inner ear, "In spite of the advances in our knowledge of the regulation of CDK activity, little is known about how regulation of CKIs is integrated into specific developmental programs to coordinate cell proliferation with morphogenesis." (Chen et al. p 1582, first column). To provide a treatment effect for a disease or disorder of the inner ear, as claimed, it would require not only hair cell proliferation, but additionally differentiation, maturation, functional recovery and maintenance of the sensory cells. Although the specification demonstrates a role for one particular cell cycle kinase inhibitor in sensory cell development, the signaling pathways had not been elucidated to achieve control of the development of these cells

in a specific manner and it was unclear whether the release of cells from inhibition of proliferation would initiate the further events required to complete the hair cell regeneration process (see for example, Löwenheim et al., PNAS, 96, 1999, page 4088, last paragraph), as would be required to achieve a treatment effect for a disease or disorder of the inner ear. The specification has not provided any guidance by which one skilled in the art would know how to administer inhibitors for cell cycle inhibitors to control this process, in order to provide a treatment effect. Further, the preferred target for inhibition in the specification, $p27^{Kip1}$, appears to have roles not only in development, but also in cell maintenance (see for example, Chen et al.). The specification has not provided any information on how to specifically inhibit $p27^{Kip1}$ for regeneration, without affecting its role in cell maintenance, such that the outcome of administration of an inhibitor would be a treatment for a disease or disorder. Given the complexity of the pathways of sensory cell development, and the lack of available information on the timing and role of cell cycle inhibitors in these pathways, the skilled artisan would not be able to predictably control the development of these cells by administering inhibitors of cell cycle inhibitors, such that a treatment effect for a disease or disorder of the inner ear would be achieved, with out undue trial and error experimentation.

In addition to the problems specific to the treatment of inner ear disorders, the claims would encompass antisense and gene therapy methods of treatment. At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al.

(Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

The specification has provided no guidance on how to administer antisense to a subject, to specifically target cells of the inner ear and treat a disease of condition of the inner ear using antisense, gene therapy or any other nucleic acid based therapy. The

field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect, including cells of the inner ear. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver nucleic acid based therapeutics, including antisense, to a target cell or tissue *in vivo* (whole organism) at a concentration effective to treat the broad range of inner ear diseases and disorders encompassed by the claims.

In order to practice the invention as claimed, the skilled artisan would need to under undue trial and error experimentation to determine how to control sensory cell development by administering inhibitors of cell cycle inhibitors, for example, which inhibitors to target for particular diseases and disorders, how to specifically target a particular cell cycle inhibitor, how long to administer a particular inhibitor, how to specifically deliver nucleic acid based inhibitors, and when to turn off and on particular cell cycle inhibitors to achieve a particular morphology, for example, in order to provide a treatment effect. Therefore, due to the breadth of the claims, the nature of the invention, the unpredictability recognized in the art, the lack of specific guidance and working examples in the specification and the quantity of experimentation required for the skilled artisan to practice the claimed invention, one skilled in the art would not be enabled to practice the claimed methods of treatment.

In response to the rejection of claim 29 under 35 USC 112, first paragraph, set forth in the prior Office action, mailed 09-10-02, Applicant argues that the claim is

enabled by the application in view of the knowledge of one skilled in the art at the time of filing. These arguments have been considered as they apply to the rejection of claims 28, 29, 31-48, 55-58 and 62 under 35 USC 112, first paragraph, set forth herein.

Applicant argues that the specification provides explicit guidance on specific disease or disorders that can be treated by the claimed methods because the specification states the diseases or disorders that are a cause of partial or complete hearing loss and are linked to damage or destruction of sensory cells. Applicant argues that the specification provides guidance on specific cell cycle inhibitors to be targeted by stating that the cell cycle inhibitors are present in the inner ear and expressed in terminally differentiated cells to prevent reentry of the cells into the cell cycle. Applicant argues that the specification indicates three cyclin-dependent kinase inhibitors to target, $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$.

These arguments have been considered as the apply to the rejection under 35 USC 112, first paragraph, lack of enablement, set forth herein, but are not found to be persuasive. The guidance Applicant indicates in the specification is not considered to be specific. The specification states the symptoms and outcome of the diseases and disorders to be treated, however, it has not provided guidance on what those diseases and disorders are, which diseases and disorders within the very broad genus of diseases causing these symptoms would derive benefit from the claimed methods of treatment and what particular active ingredients provide benefit for a particular disease or condition and what particular cyclin-dependent kinase inhibitor to target for a particular disease or condition. Applicant has described the location of expression and

activity for cyclin-dependent kinase inhibitors to target in the claimed invention, but this guidance is not specific, for example, the specification has not taught what cyclin-dependent kinase inhibitors are present in the inner ear and expressed in terminally differentiated cells to prevent reentry of the cells into the cell cycle or which of these cyclin dependent kinase inhibitors can be targeted for a particular disease or condition. Although the specification provides specific guidance to target $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$, there is no guidance on what particular diseases or conditions can be treated by inhibiting any of these proteins. For example, there is no guidance on what diseases or conditions result from overexpression of $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$, what diseases or conditions may be treated by inhibition of $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$ even under normal expression conditions.

Applicant further argues that no undue experimentation is required to control the development of sensory cells by administering an inhibitor of cell cycle inhibitors. Applicant argues that Chen et al., cited to support the rejection of record, states that $p27^{Kip1}$ provides a link between developmental control of cell proliferation and the morphological development of the inner ear, which is the main finding of Chen et al. Applicant argues that the specification also describes that genetic deletion of $p27^{Kip1}$ results in on-going proliferation in the organ of Corti and new hair cell production. Applicant argues that the results in the specification demonstrate inhibiting $p27^{Kip1}$ results not only in supporting cell proliferation, but also hair cell differentiation.

These arguments have not been found to be persuasive because the arguments do not address the scope of the claimed invention. The claimed invention is directed to

encompass methods and processes for the treatment of diseases or disorders of the inner ear by partially inhibiting or eliminating the action of at least one cell cycle inhibitor using an active ingredient. Applicant's arguments are directed to one species within a very broad genus, $p27^{Kip1}$. Read as a whole, Chen et al. supports the rejection of record in that Chen et al. teach the complexity of cell cycle regulation in hair cells and supporting cells in development and support that even after the filing date of the instant application "In spite of the advances in our knowledge of the regulation of CDK activity, little is known about how regulation of CKIs is integrated into specific developmental programs to coordinate cell proliferation with morphogenesis." (Chen et al. p 1582, first column). Although Chen et al. have provided evidence that p27Kip1 has a role in developmental control of cell proliferation and morphological development of the inner ear, the role of other cell cycle inhibitors has not been defined and Chen et al. support that, even post-filing, control of cell proliferation is poorly understood. Further, Applicant's experiments have not demonstrated that administration of an inhibitor of any other cell cycle inhibitor would provide for cell proliferation and maturation. Additionally, even for $p27^{Kip1}$, these experiments do not address how inhibition of $p27^{Kip1}$ is involved in the treatment of the broad range of diseases encompassed in the claims. For example, it is unclear whether inhibition of $p27^{Kip1}$ would provide a proliferation and maturation of cells for all diseases and disorders, for example, wherein a disease is caused by an abnormality in the cell cycle upstream of $p27^{Kip1}$.

Applicant argues Applicant argues that the reference Pfister et al., as cited in the rejection of record, addresses the clinical availability of treatments for humans and that

clinical testing and FDA approval are not a prerequisite for patentability. This argument is not found to be persuasive because Pfister et al. is cited in the rejection to demonstrate the state of the art. The claimed invention is directed to a method of treatment and Pfister et al., along with the other references cited in the rejection, supports that the state of the art, even post-filing, was that treatment methods as claimed were not available.

Applicant argues that the contrary to the assertion that antisense and gene therapy methods are unpredictable, the declaration filed March 11, 2003 demonstrates inhibition of $p27^{Kip1}$ in vitro and in vivo using antisense. The Declaration under 37 CFR 1.132 filed March 11, 2003 is insufficient to overcome the rejection of claims of 28, 29, 31-48, 55-58 and 62 based upon 35 USC 112, first paragraph, as lacking enablement, as set forth for claim 29 in the last Office action because: The Declaration does not address to scope of the claims. The experiments provided in the Declaration demonstrate inhibition of one cell cycle inhibitor using antisense delivered locally to the ear and the result is proliferation of cells in the organ of Corti in two out of five test animals. This does not address the scope of the claims which include systemically delivered antisense and gene therapy vectors, are directed to methods of inhibition of any cell cycle inhibitor and require a treatment effect for a broad range of diseases and disorders. The Declaration does not provide any guidance or evidence for the inhbition of any other cell cycle inhibitor, nor does it demonstrate a treatment for the broad range of diseases encompassed in the claims and it does not address administration of any active ingredient systemically.

Applicant cites other references, published after the priority date of the instant Application, to support that antisense and vectors have been delivered to the ear. Applicant argues antisense has been used for therapy in other sensory systems, like the eye using Vitravene. This has not been found to be persuasive because each of the references cited by Applicant to support predictability of antisense are directed to methods wherein antisense and vectors are delivered locally to the ear. Vitravene is delivered locally by direct injection in the eye.

Claims 28, 29, 31-48 and 55-58 are maintained as rejected and claim 62 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 28, 29, 31-48 and 55-58 are drawn to active ingredients that inhibit the activity of a cell cycle inhibitor present in the inner ear, and methods that require these active ingredients. These active ingredients claimed, and methods claimed that require these active ingredients, encompass a very broad genus of compounds with highly variant structures. For example, the genus of active ingredients would encompass many types of inhibitors, including proteins, peptides, nucleic acids encoding proteins, inhibitory nucleic acids, small molecule inhibitors, and antibodies, and would encompass direct or indirect inhibitors of cell cycle inhibitors, each of which would have a different structure. Further, the genus of active ingredients would encompass

inhibitors of a very broad genus of cell cycle inhibitors and cyclin dependent cell cycle inhibitors; inhibitors of various cell cycle inhibitors would vary widely in structure.

The specification has not provided the structure of any active ingredient encompassed by the claims. For example, although the specification suggests the preferred embodiment of the claimed active ingredients would be inhibitors of $p27^{kip1}$, the specification has not provided any structure for inhibitors of $p27^{kip1}$, for example, there is no sequence for an antisense inhibitor, no mRNA sequence by which an antisense sequence could be determined, no amino acid sequence or structural information for a peptide inhibitor of $p27^{kip1}$, and not structural information has been provided for a small molecule inhibitor of $p27^{kip1}$. Additionally, the specification has not provided any information about what other cell cycle inhibitors would be inhibited to provide sensory cell regeneration, or the structure of active ingredients inhibiting these cell cycle inhibitors. The genus of active ingredients claimed is so broad that it may encompass compounds known in the prior art, generally any inhibitor of a cell cycle inhibitor, however, the specification has not provided sufficient description such that the skill artisan would recognize which prior art compounds have the desired activity, nor does the prior art provide a written description for the very broad genus claimed.

The specification has not provided the detailed chemical structure or common structural characteristics of these active ingredients, such that the skilled artisan would recognize that the inventor was in possession of the broad genus of active ingredients claimed, or required to practice the claimed methods, at the time the instant invention was made.

In response to the rejection of record under 35 USC 112, first paragraph, lack of adequate written description, set forth in the prior Office action mailed 09-12-2003, Applicant argues that since the claims are not directed to any nucleic acid sequences or amino acid sequences the written description requirement can be met without disclosing specific sequences. Applicant argues that the written description requirement may be met by disclosure of functional characteristics when coupled with a known or disclosed correlation between structure and function according to Enzo Biochem. V. Gen-Probe Inc. Applicant argues that functional characteristics of the active ingredients used in the claimed methods are well defined and there are many known correlations between the function of inhibiting the action of a cell cycle inhibitor and structure. Applicant cites Coates et al. and Hauser et al. as disclosing antisense, protein and antibody inhibitors of $p27^{Kip1}$ and therefore the skilled artisan would recognize possession of the claimed invention. This is not found to be persuasive because Applicant is claiming antisense and amino acids because claims 55 and 56 are directed to compositions and encompass nucleic acids and amino acids. Further, the claimed methods of treatment require the active ingredients, which include nucleic acids and amino acids however, the genus of these active ingredients have not been described. Applicant has not demonstrated how the facts of Enzo Biochem v. Gen-Probe Inc. are similar to the instant case. In the instant case, the structure of the broad genus of compounds does not correlate with function. The genus is extremely broad, encompassing many different types of compounds of variant structure and targeted to a broad range of target

proteins, which have not been identified, and, therefore, the function of inhibiting the broad range of target cell cycle inhibitors would not describe the broad genus of active ingredients. Further, the species of inhibitors described by Coats et al. and Hauser et al. are directed to inhibitors of one cell cycle inhibitor, $p27^{Kip1}$, and do not describe the genus of compounds encompassed in the compositions claimed and used in the methods of treatment claimed.

Claim Rejections - 35 USC § 101

The rejection of record of claims 28, 31-53 and 57-60 under 35 U.S.C. 101, set forth in the prior Office action, mailed 09-10-02, is withdrawn in response to Applicant's amendments filed 03-11-2003.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 55 and 56 are maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Hauser et al. (Cell Growth and Differentiation, Vol. 8, Feb 1997, p 203-211).

Hauser et al. disclose nucleic acids inhibitors of cell cycle inhibitors, including antisense targeted to $p27^{kip1}$ in a solution comprising a pharmaceutically acceptable carrier (for example, a solution comprising water, KBM media, see for example page

210, second column). Hauser et al. do not disclose that these inhibitors have sensory cell regeneration properties, however, these inhibitors have all of the characteristics of the claimed active ingredients and are active against $p27^{kip1}$, the preferred embodiment of the instant specification and, therefore, would inherently have the activity claimed. The specification is silent with regard to the concentration of antisense required to be therapeutically effective, however, the concentration of antisense in the composition disclosed by Hauser et al. is effective for inhibition of $p27^{kip1}$, which is the effect set forth in the specification for a therapeutic effect and is at a concentration higher than the concentration used in Applicant's declaration submitted March 11, 2003, and therefore, would be considered to be in a therapeutically effective amount. Therefore, Hauser et al. anticipates claims 55 and 56.

In response to the rejection under 35 USC 102(b) as anticipated by Hauser et al. in the prior Office action, Applicant argues that the amendments filed March 11, 2003 have overcome the rejection of record because Hauser et al. does not disclose or teach a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an inhibitor of a cell cycle inhibitor.

This argument has not been found to be persuasive because Hauser et al. does disclose their oligonucleotide in a composition comprising a pharmaceutically acceptable carrier; for example, the oligonucleotide is in KBM media, which comprises water. Further, the composition disclosed by Hauser et al. meets all of the physical limitations of the claimed composition and, therefore, would be expected to have any

pharmaceutical properties of that composition, particularly since the composition disclosed by Hauser et al. inhibits $p27^{kip1}$, which is the mechanism proposed in the specification for the therapeutic properties of the claimed composition.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A Lacourciere

KAREN LACOURCIERE
PATENT EXAMINER

Karen A. Lacourciere
May 31, 2003